Spheres of Influence

Trial and Error: Should Pregnant Women Be Research Subjects?

Scientists, policy makers, bioethicists, and the public are currently split on an issue that cuts to the heart of scientific research and draws into the purportedly objective, rational world of science people's passionate views on personal autonomy: whether federal research guidelines that bar pregnant women, and in effect their fetuses, from clinical trials protect or discriminate against women.

The federal government is preparing to respond to growing pressure to change protectionist laws and give women greater control over their own health. In March 1994, the Institute of Medicine (IOM), a division of the National Academy of Sciences, issued a report urging current law to be changed. If adopted by the federal government, the IOM's recommendations would clear the way for a pregnant woman to participate in medical drug experiments, for conditions related or unrelated to pregnancy, even when the safety of her fetus cannot be assured.

New medical treatments are rarely tested on pregnant women for safety and efficacy, including drugs such as analgesics, psychoactive agents, antimicromobials, diuretics, and cough medicines reportedly used by three out of four pregnant consumers. Excluding a woman from clinical trials based on her pregnant status could be deemed discriminatory by denying her the benefits of scientific discovery. In addition, pregnant women offer a fertile area for research on environmentally mediated diseases, many of which affect the reproductive system in particular or cause abnormalities in children of parents exposed to environmental toxins.

Experimentation on pregnant women can produce unexpected results because of the numerous physiological changes during pregnancy that alter the body's disposition of drugs. According to IOM, these physiological changes include increased plasma volume, body weight and body fat, metabolism, and hormone levels that can decrease the concentration of a drug in the body and its therapeutic effects. Moreover, reliance on reporting of adverse effects by clinicians does not provide sufficient data to assess the safety and effectiveness of drugs for pregnant women. "The basic presumption is that a woman who may become pregnant can get information about an agent and can make an informed decision," said Anthony Schialli, a reproductive toxicologist and director of the residency program at Georgetown University Medical Center. "But information for a new drug she takes consists of interpreting animal data . . . which is the same as the risks for environmental agents . . ." One scientist involved in the IOM report stated, "Our approach was driven by the fact that there are not enough proven safe treatments for pregnant women who become ill during pregnancy or even before with diabetes, hypertension, a cold, an allergy, or preterm labor."

The 16-member panel of the IOM unanimously supported the participation of pregnant women in research studies as a right and urged that studies include rather than exclude them. The bottom line in IOM's resolution boils down to the issue of informed consent. The IOM committee said a pregnant woman, like any research subject, must be given complete disclosure of the risks and benefits to which she may be exposing herself and her unborn baby, preferably by her health care provider.

Among the panel's recommendations are the following:

- Even when evidence is unknown or ambiguous, the decision about acceptability of risk to the pregnancy or offspring should be made by the woman as part of the informed consent process;
- Pregnancy, contraception, and termination options should be discussed as part of the consent process in clinical studies that pose unknown or unforeseeable risks to the unborn child;
- Where risk of significant harm to a pregnant woman or her fetus is known or can be plausibly inferred, investigators and the IOM Institutional Review Board (IRB) should have the final say;
- NIH should advance clinical research for the management of three categories of medical conditions that may threaten the successful course of pregnancy: preexisting (e.g., lupus); during (e.g., gestational diabetes); and those that affect pregnancy outcome (resulting in preterm labor, for example).

"This report, in its insistence on respecting the rights of the person, goes further than the research community had agreed on," said Daniel Federman, co-chair of the IOM panel and dean of medical education at Harvard Medical School. However, Federman admitted that a major bone of contention within the committee and more broadly the scientific and public policy communities was the issue of setting limits on a pregnant woman's role in clinical trials when there is no prospect of medical benefit to her and a risk of significant harm to potential offspring.

"Some of the committee worried that [the restriction] leaves an opening through which [the IRB] can justify a diminution of her autonomy. We took that concern seriously but as a group were not unanimous for giving absolute autonomy to the pregnant person," Federman said. No such restrictions exist for her male counterpart, although the IOM report noted that scientists have long suspected that offspring may be at risk because of exposure of the father as well. These risks include spontaneous abortion, stillbirth, impaired growth, and structural and functional abnormalities as a result of environmental and other exposures.

For example, at recent congressional hearings on Persian Gulf syndrome, several men testified that their exposure to chemical warfare or other agents had adverse effects on their offspring. Yet, according to Vivian Pinn, director of the NIH's Office of Research on Women's Health, which contracted the IOM study, male-mediated toxicity in medical experimentation is deprecated. "Not as much attention is paid to the possible effects of the male on the fetus, and yet the sperm goes with the ova . . . and we should know exactly what effect it has," Pinn said.

The IOM report noted that bringing pregnant women into clinical studies poses new complications, dangers, and a sticky dilemma: by including pregnant women in clinical trials, fetuses are exposed to the risk of teratogenicity; by excluding them the scientific community and public lack hard facts on how various drugs or environmental toxins affect a pregnant woman and her fetus.

At the NIEHS, where many studies focus on reproductive toxicity, there is no consensus about the ideal way to gather these facts. During a recent exchange, some NIEHS scientists argued that existing federal rules against experimenting on pregnant women are beneficial to protect a fetus and prevent exploitation.

Alan Wilcox, chief of the NIEHS's epidemiology branch, whose landmark epidemiological studies have examined the effects of diethylstilbestrol on the offspring of women who took the drug during pregnancy, is, like many scientists, ambivalent. While there is "no prospect of the NIEHS

[testing environmental toxins on pregnant women], and the issue has not yet come before the institute," Wilcox said, the case for involving pregnant women in clinical trials of untested medications is persuasive.

Protectionists part company with the IOM panel on the issue of a woman's personal autonomy. "If not paternalistic, then what is exclusion?" asked Ruth Macklin, a professor of epidemiology and social medicine at Albert Einstein College of Medicine in New York. "Why should some distant scientist whose relationship lasts a brief time make the ultimate determination rather than a woman who presumably cares more about her unborn child?"

Current law classifies pregnant women as vulnerable subjects worthy of special protection, along with fetuses, prisoners, the mentally disabled, and children, who may only occasionally participate in trials. But the IOM report views this distinction as "suggesting that pregnant women are less autonomous or more easily exploited than other persons—an inference that the committee has found no evidence to support." Curtis L. Meinert, director of the Center for Clinical Trials at the Johns Hopkins University School of Hygiene and Public Health, agrees with the report and questions the special status of pregnant women. Meinert would not rule out recruiting pregnant research subjects.

Federal agencies such as the National Institutes of Health and the Food and Drug Administration are deciding whether to revamp protectionist regulations implemented in the 1970s to enable women of childbearing age, fetuses, and children to participate in drug experiments and research studies that could have benefits for both them and society. If approved by the federal government, the amended regulations could require investigators to include a pregnant woman in their studies to test a new therapy unless her exclusion could be justified. But there may also be less radical options.

William Dommel, chair of the Public Health Service's Human Subject Regulation Drafting Committee, said that the committee is reviewing events that led up to the rules' enactment beginning with the Nuremberg trials. According to Dommel, more recent milestones such as the IOM report, FDA's revised guidelines on research involving women, and the NIH Revitalization Act of 1993 will also be reviewed.

The regulations pertaining to research, development, and related activities involving fetuses, pregnant women, and human *in vitro* fertilization "have not been reviewed for more than 15 years," said Dommel, who indicated that the drafting committee's work is dependent, in part, on the NIH Human Embryo Panel's recommendations. "We are . . . looking at what, if any, changes are needed with respect to research involving testing on these populations, and the NIH panel will make its recommendations and complete their work before we begin working on actual changes," he added.

The FDA's Center for Drug Evaulation will meet sometime this fall to "look at these issues around pregnant women and clinical trials . . . " according to Ruth Merkatz, special assistant on women's health issues to FDA Commissioner David Kessler. The agenda will include "collecting information on the use of drugs and other products in pregnancy, under what circumstances trials could and would be done, and how data is collected on women [as research subjects] in pregnancy," Merkatz said.

Meanwhile, the Office of Research on Women's Health is on the fence. The NIH inclusion guidelines charge ORWH with ensuring that all women of childbearing years are well represented in research studies, including clinical trials, for diseases that affect them. ORWH officials also serve on the groups reviewing DHHS regulations to examine all issues relating to including pregnant women in clinical studies. "We need the information, but obtaining it can have great risks to both mother and child . . . and all issues must be considered—both immediate and longterm," said ORWH Assistant Director Judith LaRosa. "Participating in a clinical trial may be a mother's choice, but at what point does a fetus have a say in the matter?"

Lionel B. Edwards, formerly assistant vice president of international clinical research at Hoffman-LaRoche, contends that few women will "spontaneously volunteer themselves or their offspring unless they are dying, so the majority of trials won't get enough women to participate anyway."

Karen H. Rothenberg, director of law and health care programs at the University of Maryland School of Law, restates the question that confounds attempts to resolve this issue: "Do you then say, okay, as a class, women are excluded or as a class they are entitled to be included?" Rothenberg points to a landmark Supreme Court decision, the Johnson Controls case, which upheld a woman's right, rather than her employer's, to decide whether or not to expose her fetus to workplace environmental hazards and preempt tort claims brought by children allegedly injured by their mothers' exposure as evidence supporting a woman's right to decide to participate.

Ellen Wright Clayton, an assistant professor of pediatrics and assistant professor of law at Vanderbilt University, thinks it unlikely that children injured before birth due to their parent's participation in research would have grounds to sue. "Looked at simply from the perspectives of legal doctrine and extensive disclosure that typically occurs in the research setting, there will rarely be any basis for successful lawsuits by children or particularly by parents." However, Clayton argues that proposals to limit or ban drug manufacturers' liability for injuries "seems unjust" and argues that the potential costs of liability should be borne by manufacturers as the costs of seeing that new products are fully tested before they are brought to market.

Environmental law specialists Ellen Flannery and Sanford Greenberg with the law firm of Covington and Burling in Washington, DC, think companies have more to worry about by excluding pregnant women from trials. They claim women who are harmed by a commercial product would have less grounds to sue manufacturers who included them in clinical trials than those who left them out. Rothenberg contends that the manufacturers of diethylstilbestrol lost because they had not done their homework. "Litigation did not result from clinical trials, except at the University of Chicago where there was a lack of informed consent about the drug's risks," Rothenberg said. "If they had looked at the data and done adequate trials, [the companies] may never have marketed [diethylstilbestrol]."

Edwards, former chair of special populations for the Pharmaceutical Manufacturers Association, said the industry sees the changing rules as a "social readjustment" and is "happy to go along with the consensus," but cautions, "If excluding pregnant women [means] according to the regulations you could have a grant withheld or withdrawn, that's another story. Don't subgroup us to death or we'll never get a drug out the door."

Merkatz thinks pregant women should not be summarily dismissed from research if the probable risk is clearly explained and their participation can further scientific knowledge. In a July 1993 article that appeared in the *New England Journal of Medicine*, she points to substantial ethical and legal precedent: "Ethical principles articulated in the Belmont report—respect for persons, beneficience and justice—as well as recent actions by the Congress and decisions by the U.S. Supreme Court suggest that women should have the right to make their own risk–benefit choices about their pregnancies."

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